Phenotypic variability between brothers with Barth syndrome: one with severe neonatal presentation and one with late infantile presentation

Stephanie Campbell, Shagun Kaur, Kara Pappas
Children’s Hospital of Michigan, Central Michigan University School of Medicine

Introduction

- Barth syndrome is a mitochondrial disorder caused by a mutation in the TAZ gene, leading to a deficiency in the cardiolipin remodeling enzyme.
- Clinical manifestations include cardiomyopathy, skeletal myopathy, neutropenia, and poor growth/short stature.
- There is considerable variability in the age of onset, severity of clinical manifestations, and progression of symptoms.
- Studies have not found any genotype-phenotype correlation for Barth syndrome\(^1,2\).
- We report 2 brothers with a clinical, biochemical and molecular diagnosis of Barth Syndrome with significant phenotypic discrepancy
- One brother was born with significant cardiac pathology including a circular shunt

Patient Overview

Older Brother

- Presented at 10 months with dilated cardiomyopathy
- Found to have failure to thrive and neutropenia.
- Biochemical labs: increased urine 3-methylglutaconic and 3-methylglutaric acids.
- Molecular testing revealed a likely pathogenic variant (c.109+5G>A) in the TAZ gene.
- This patient’s chronic systolic heart failure remained stable on medication, with normal growth and development.
- At 2 years old, he developed decompensated heart failure.
- He developed cardiogenic shock, ischemic and necrotic limbs, liver failure, fungal sepsis, and subsequently passed away due to respiratory failure.

Younger Brother

- No prenatal testing done
- Anatomic ultrasound at 27 weeks was reportedly normal with no prenatal echocardiogram performed.
- Born at 39 weeks and was limp, requiring resuscitation and chest compressions at delivery. Intubated at birth
- Cardiac findings: circular shunt (on next slide)
- Molecular testing resulted with the same variant (c.109+5G>A).
- Developed increasing lactic acidosis, kidney failure, and liver failure.
- Suspected necrotizing enterocolitis, possibly secondary to mitochondrial dysfunction of gut.
- Underwent pulmonary valve occlusion to create a single ventricle system but clinical condition did not improve.
- Not an ECMO or heart transplant candidate due to multi-organ failure, and subsequently passed away at 6 weeks of age.
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Cardiac findings in case 2: Dysplastic tricuspid valve with no forward flow, patent foramen ovale with right to left flow, large patent ductus arteriosus with left to right flow, stenotic and regurgitant pulmonary valve) with depressed biventricular function.

Figure 1. Schematic of younger brother’s congenital heart defect

Conclusion

This case report emphasizes the complex cardiac pathology that can occur as well as the intrafamilial phenotypic variability possible in Barth syndrome.

References
